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1879-1961

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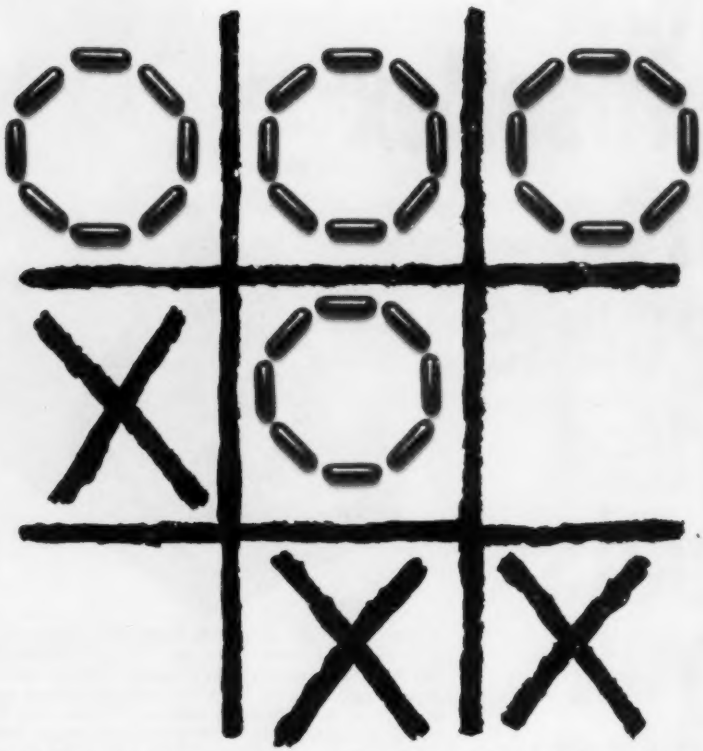

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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IN MEMORIAM*

DR. E. FULLERTON COOK

1879-1961

THE death of Dr. E. Fullerton Cook on March 2nd. of this year brought to a close the life of one of the true stalwarts of American Pharmacy and, to those who knew him well, his description as "a salwart" will be recognized for the aptness of its selection.

Dr. Cook received his first degree in pharmacy from the Philadelphia College of Pharmacy and Science in 1900 where, immediately after his graduation, he became a true disciple of the great Joseph P. Remington with whom he worked and served until Dean Remington's death. It was a natural consequence that Dr. Cook would succeed to many of the challenging tasks in behalf of pharmacy which Remington himself had held and, thus, he became co-editor of *Remington's Practice of Pharmacy*, Professor of Pharmacy and Director of the Operative Pharmacy Laboratories, and was even elected Chairman of the Revision Committee of the Pharmacopeia immediately upon his election to the Revision Committee itself. In this latter capacity, he served the Pharmacopeia through five revisions and did so with a dedication and a talent for bringing various groups together which brought him the respect of government and industry, as well as the many physicians, pharmacists, and chemists with whom he worked.

Dr. Cook's interests were not confined to the affairs of pharmacy in the United States since he was known and loved by former students and friends in almost every nation of the world. He also served as one of the experts called together by the League of Nations in 1938 to seek more uniform international drug standards and continued this work when it was again taken up by the World Health Organization of the United Nations.

Dr. Cook was a man of great tenacity of purpose and that which he set as his goal to accomplish he never failed to achieve regardless

* The Editor this month dedicates this issue to Dr. E. Fullerton Cook who for many years was associated with this Journal and a member of its Committee on Publication.

of the time and effort which were required. It was in this spirit that he was largely responsible for moving the Philadelphia College of Pharmacy and Science from its old center-city location to its new building in West Philadelphia, first occupied in 1927, and again in his almost singlehanded effort in seeing to it that the Pharmacopeia which he loved was properly housed in its present beautiful headquarters on Park Avenue in New York.

Of all the honors which came to Dr. Cook during his long life, none meant more to him than receiving the Remington Medal in 1931, for he bore for Remington, his former teacher and preceptor, a respect which bordered on reverence.

Dr. Cook continued to be active to the very last days of his life and the Twelfth Edition of the *Remington's Practice of Pharmacy* recently released was prepared with Dr. Cook serving as one of the working editors in this rather monumental task. He was also an active member of the Board of Trustees of the Philadelphia College of Pharmacy and Science. It would have been difficult to have seen Dr. Cook other than alive, vibrant, and full of energy and it is indeed a blessing that he continued active and alert almost to the end. He was truly a stalwart and a worthy member of that group of distinguished individuals to whom American Pharmacy owes so much. History will record in Pharmacy's Hall of Fame the name of E. Fullerton Cook as of the same distinction as Procter, Remington, Wood, Maisch, and La Wall. His was a life well lived and a name to be remembered.

L. F. Tice

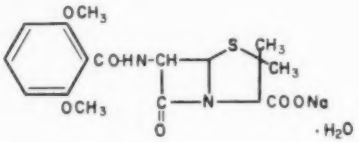
NEW DRUGS OF 1960

By L. F. Tice *

It is the purpose of this review to discuss briefly the most important new prescription drugs released during the year, 1960. It is presented to assist pharmacists and physicians in their unending task of keeping well informed on these, the continuing results of intensive pharmaceutical research.

Anti-Infectives

THE most interesting development in the field of anti-infectives during 1960 was the preparation of a new penicillin having what appears to be a highly specific antibacterial action against resistant strains of staphylococci. This new penicillin can be described as sodium 6-(2'-6'-dimethoxybenzamido) penicillanate monohydrate or, more simply, as sodium 2,6-dimethoxyphenyl penicillin monohydrate. The generic name is dimethoxyphenecillin. It is available as Staphcillin (Bristol) and Celbenin (Beecham). This new penicillin is unique in that it does not seem to be affected by penicillinase of staphylococcal origin. It has given very good results in treating most cases of in-



DIMETHOXYPHENECILLIN

STAPHCILLIN (BRISTOL)

CELBENIN (BEECHAM)

* Lecturer on the Pharmacy and Chemistry of Medicinals and Dean of Pharmacy, Philadelphia College of Pharmacy and Science.

fections caused by strains of staphylococci resistant to other penicillins, including phenethicillin, as well as other antibiotics. Since it is very unstable in an acid medium, it cannot be used effectively except by the parenteral route. The dose is 1 Gm. intramuscularly every 4-6 hours or, if given intravenously, 1 Gm. every 6 hours, the drug in the latter case being dissolved in 50 ml. of normal saline and administered at a rate not exceeding 10 ml./min.

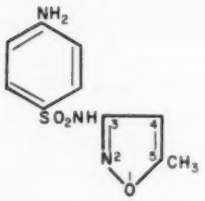
Dimethoxyphenecillin is not recommended for use against organisms susceptible to other penicillins, nor should it be used in persons known to be sensitive to other penicillins.

The antibiotic, paromomycin (Humatin—Parke Davis) is another of those derived from a strain of Streptomyces. It has been found to possess useful antibacterial action in enteric infections caused by *Shigella, Salmonella, E. coli,* and also in nonspecific diarrheas and dysenteries. It is also very useful in intestinal amebiasis and preoperatively to suppress the intestinal flora. Humatin is not appreciably absorbed from the intestinal tract and is only given orally. The oral dose varies with the condition to be treated. It is supplied in 250 mg. capsules as the sulfate.

A number of antibiotics are currently on clinical trial including Aspartocin (Lederle); Streptovaricin (Upjohn), having marked tuberculostatic activity; Streptozotocin (Upjohn); Thiomycetin (Winthrop), an analog of chloramphenicol; and Leucomycin (National Drug).

The use of nystatin to prevent the development of moniliasis during tetracycline therapy is well established. Recently, E. R. Squibb released a combination of phosphate potentiated tetracycline and amphotericin B under the name, Mysteclin "F". This combination utilizes the antimonilial action of amphotericin B which E. R. Squibb also markets as Fungizone.

The development of the lauryl sulfate salt of the propionyl ester of erythromycin by Eli Lilly initially was for the purpose of preparing a tasteless suspension for pediatric use. Further study of this salt showed it to be superior to the ester itself in its acid resistance and resulting blood levels when taken orally. As a result of this finding, both Ilosone (Lilly) and Ilosone-Sulfa (Lilly) are now prepared using the lauryl sulfate, the older products having been replaced in trade stocks.



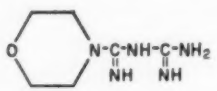
Ro-4-2130

5-METHYL-3-SULFANILAMIDO-ISOXAZOLE

In the field of sulfonamides, a new compound, Ro-4-2130, is under clinical investigation by Roche. It is 5-methyl-3-sulfanilamido isoxazole. This is closely related to sulfisoxazole (Gantrisin—Roche) differing in having one less methyl group attached to the isoxazole ring and in having a different position of attachment of this ring. The drug is reported to have given excellent results in acute streptococcal pharyngitis.

The well-known antibacterial agent, nitrofurantoin (Furadantin —Eaton), is now available as its sodium salt for intravenous infusion. It is supplied as sterile crystals (Furadantin Sodium—Eaton) in vials containing 180 mg. which are dissolved in 500 cc. of a suitable intravenous fluid. This product replaced that previously available wherein the drug was solubilized using a polyethylene glycol, and it is claimed to be superior to it.

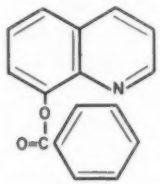
Considerable interest is being shown in one of the first antiviral agents to be marketed. This is N,N′-anhydrobis (β-hydroxyethyl) biguanide hydrochloride. The compound was developed by the Kabi Research Institute in Stockholm. It is being marketed in England as Virugon (Bayer Products) and is under clinical study in this country by SKF Laboratories. Known also as "ABOB", this compound is claimed to be effective in the prophylaxis and suppression of influenza.



VIRUGON (BAYER)

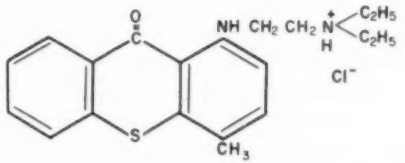
It is also being studied for possible use in several other viral diseases including herpes simplex, herpes zoster, mumps, and measles. As marketed by Bayer, Virugon tablets contain 100 mg. of the antiviral agent plus 0.1 mg. each of atropine methylnitrate and scopolomine methylnitrate. The dose is 2 tablets 3 times daily for 7-10 days. For prophylaxis, the dose is 1 tablet 3 times daily.

A topical antifungal agent recently described is 8-quinolinyl benzoate. A 0.25 per cent solution is claimed to be fungicidal after 2 minutes to several species of fungi involved in dermatophytoses of the human skin including *T. gypseum, T. mentagrophytes, M. audouini, M. canis,* and *M. fulvum.*



8-QUINOLINYL BENZOATE

A new non-metallic agent for use in schistosomiasis was released last year by Burroughs Wellcome. Chemically, it is 1-β-diethylamino-ethylamino-4-methyl thioxanthone hydrochloride. It is supplied as Lucanthone (B. W.) and is a yellow powder having moderate solubility in water. The drug is given orally in a dose of 15 mg./Kg./day divided in 3 doses and given for 7 consecutive days. It is believed to

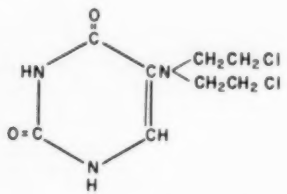


LUCANTHONE (B.W.)

act against the adult forms and to interfere with egg production. Lucanthone is most effective against *S. mansoni* and *S. hematobium* infections and less so against *S. japonicum*. Side-effects may occur including nausea and tremors. Overdosage may cause convulsions and chronic toxicity involves hepatic and renal damage. Lucanthone has the advantages of being non-metallic and effective orally after short-term therapy.

Antineoplastic Agents

The search for more effective antineoplastic agents continues but with no important "breakthroughs" which have reached the product stage. Among the alkylating agents reported last year were epoxypropidine (Lilly) and Uracil Mustard (Upjohn). The latter is 5-bis (2′-chloroethyl) aminouracil. By combining the alkylating chloroethyl groups with uracil, the intent is to increase the affinity of the compound for tumor cells which are known to utilize uracil. Uracil Mustard in clinical trials has given good results, particularly in lymphomas and chronic leukemias. Occasionally, solid tumors and particularly ovarian carcinomas responded. The advantages cited were: small dosage required, uniform tolerability, and simplicity of regimen. It is possible that Uracil Mustard may be of value when other alkylating agents have failed.

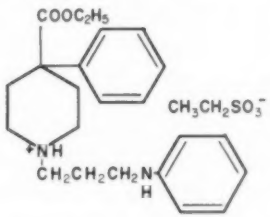


URACIL MUSTARD (UPJOHN)

Two antibiotics reported as having some anti-tumor activity are Streptovitacin A (Upjohn) and Actinomycin D (Lederle). The latter, while it has considerable activity, is highly toxic.

Analgesics and Anesthetics

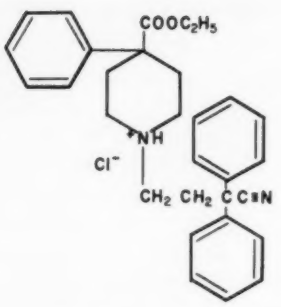
A new narcotic analgesic chemically related to meperidine is piminodine ethanesulfonate (Alvodine ethanesulfonate—Winthrop). Chemically, this is ethyl 4-phenyl-1-[3-(phenylamino) propyl] piperidine-4-carboxylate ethanesulfonate. It differs from meperidine in having a 3-phenylaminopropyl substituent on the piperidine nitrogen instead of a methyl group and it is even more closely related to anileridine (Leritine—MSD). Piminodine is claimed to have the analgesic equivalence of morphine but to cause much less nausea, constipation, euphoria, and drowsiness. It is particularly useful in terminal cancer patients since it can be given orally, does not cause any marked depression, and does not interfere with their essential activities. Piminodine is also useful preoperatively and postoperatively and for all types of severe pain. The oral dose is 25 to 50 mg. every 4-6 hours. Subcutaneously, the dose is 10 to 20 mg. The usual morphine antagonists, nalorphine and levallorphan, are antidotes for overdosage since they block all the actions of the drug. Piminodine has addiction liability as do all potent analgesics in this category.



PIMINODINE ETHANESULFONATE

ALVODINE ETHANESULFONATE (WINTHROP)

A drug closely related chemically to the meperidine group of analgesics but not used for analgesia is diphenoxylate hydrochloride (Lomotil—Searle). Chemically, this is 2,2-diphenyl-4-(4-carbethoxy-4-phenyl-1-piperidino) butyronitrile hydrochloride. Diphenoxylate is used to check acute or chronic diarrheas such as those associated with gastroenteritis, irritable bowel, regional enteritis, ulcerative colitis, and food poisoning. It acts by inhibiting excessive gastrointestinal propulsion. The dose is 10 mg. (2 tablets) 3-4 times daily for initial control, then reduced as indicated. A small amount of

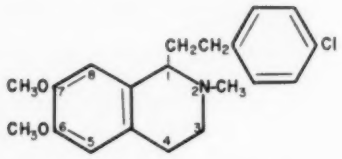


DIPHENOXYLATE HYDROCHLORIDE

LOMOTIL (SEARLE)

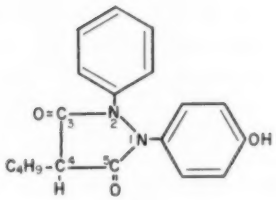
atropine sulfate (0.025 mg.) is present in each tablet as marketed to discourage overdosage. Diphenoxylate is claimed to be devoid of addiction properties and patients who have been taking it show no withdrawal reaction even when challenged with nalorphine.

A new codeine-like analgesic but an isoquinoline derivative is presently on clinical trial. It is known under the Roche experimental number Ro-4-1778/1. Clinically, it is 1-(*p*-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. It is claimed to have the same oral potency as codeine but not to possess addiction properties. The need for drugs in this category is well established as evidenced by the considerable success of d-propoxyphene hydrochloride (Darvon—Lilly) which was introduced some few years ago.



Ro-4-1778/1

An analgesic and antiarthritic closely related to phenylbutazone was recently released by Geigy. It is oxyphenbutazone (Tandearil —Geigy) and differs from phenylbutazone (Butazolidin—Geigy) only in having a hydroxy group in the para position on the N_1-phenyl sub-

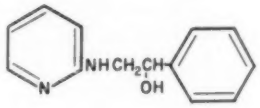


OXYPHENBUTAZONE

TANDEARIL (GEIGY)

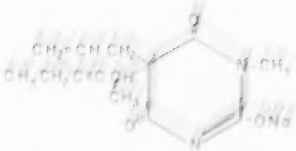
stituent attached to the pyrazolidine ring. Oxyphenbutazone was developed as a result of studies on the absorption and excretion of phenylbutazone in which it was found that the hydroxy derivative was one of its metabolites. While oxyphenbutazone has about the same biological half-life as phenylbutazone (about 3 days), it is believed to be less toxic and to offer certain clinical advantages. Oxyphenbutazone is supplied in 100 mg. tablets and it is used for the same purposes as phenylbutazone, the dose being 100 mg. 3-4 times daily reduced, if possible, once the inflammation and pain have subsided. In gouty arthritis, a somewhat more intense therapy initially is required.

An analgesic with some muscle relaxant action was introduced last year as phenyramidol hydrochloride (Analexin—Irwin, Neisler). Chemically, this is 2-(β-hydroxyphenethylamino) pyridine hydrochloride. In therapeutic doses, it is claimed to have an analgesic action equal to that of codeine and, in addition, to depress subcortical and spinal polysynaptic nerve impulses reducing muscle tone without impairing function. It is supplied as 200 mg. tablets and also as Analexin-AF which contains 100 mg. plus 300 mg. of aluminum aspirin.



PHENYRAMIDOL HYDROCHLORIDE

ANALEXIN (IRWIN, NEISLER)



METHOHEXITAL SODIUM

BREVITAL (LILLY)

A new ultra-short, intravenous barbiturate is methohexital sodium (Brevital—Lilly). Chemically, it is sodium-α-dl-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate. From its structure, it will be seen that, like certain other ultra-short acting barbiturates, it has an N_1-methyl substituent but, unlike these, its ultra-short action is not due to rapid absorption in body fat after injection but to the instability of the acetylenic side chain which is rapidly metabolized. It is for this reason that, unlike most such drugs, successive doses given to maintain anesthesia do not need to be reduced in amount. The chief advantage of methohexital is the short recovery period following cessation of its use. Methohexital sodium for the induction of anesthesia is given in an amount of 70-100 mg. (7-10 cc. of 1 per cent solution). The dosage required to maintain anesthesia is adjusted in accordance with the need of the patient or maintenance can be achieved by a carefully regulated intravenous drip.

Anti-Epileptics

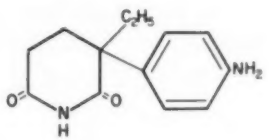
The third in its series of succinimide derivatives useful in petit mal epilepsy has been released by Parke Davis. It is ethosuximide (Zarontin—Parke Davis). Chemically, it is α-ethyl-α-methyl suc-

ETHOSUXIMIDE

ZARONTIN (PD)

cimide as compared with Milontin (P. D.) which is an N-methyl-α-phenyl derivative and Celontin (P. D.) which is the N-methyl-α-methyl-α-phenyl derivative. Ethosuximide is useful in petit mal epilepsy and sometimes controls the condition when other drugs fail or cannot be used. It is supplied in 0.25 Gm. capsules.

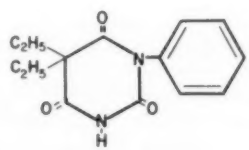
An anti-epileptic closely related to the hypnotic-sedative, glutethimide (Doriden—Ciba), is its *p*-amino derivative, aminoglutethimide (Elipten—Ciba). Chemically, it is α-(*p*-aminophenyl)-α-ethyl glutarimide. It is useful in all forms of epilepsy and often improves control when used to supplement other therapy. A skin rash frequently occurs during the early stages of therapy. This usually clears up, particularly if the dosage is kept as low as is consistent with control of the seizures. Initial dosage should be low and then gradually increased to the required level. If a rash appears and it does not clear within about a week, the drug should be discontinued. The drug is available in 250 mg. tablets.



AMINO-GLUTETHIMIDE

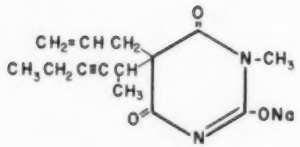
ELIPTEN (CIBA)

A new barbiturate particularly suited for the control of febrile seizures is phenetharbital (Pyrictal—Burroughs Wellcome). Chemically, it is 1-phenyl-5,5-diethyl barbituric acid. From its structure, it will be seen that it differs from barbital only in having an N_1 phenyl



PHENETHARBITAL

PYRICTAL (B.W.)



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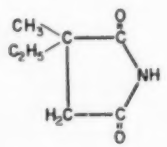
Anti-Epileptics

The third in its series of succinimide derivatives useful in petit mal epilepsy has been released by Parke Davis. It is ethosuximide (Zarontin—Parke Davis). Chemically, it is α-ethyl-α-methyl suc-

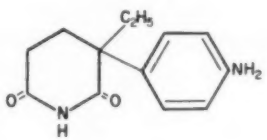


ETHOSUXIMIDE

ZARONTIN (P.D.)

cimide as compared with Milontin (P. D.) which is an N-methyl-α-phenyl derivative and Celontin (P. D.) which is the N-methyl-α-methyl-α-phenyl derivative. Ethosuximide is useful in petit mal epilepsy and sometimes controls the condition when other drugs fail or cannot be used. It is supplied in 0.25 Gm. capsules.

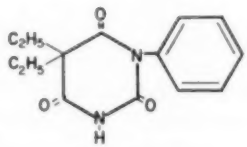
An anti-epileptic closely related to the hypnotic-sedative, glutethimide (Doriden—Ciba), is its *p*-amino derivative, aminoglutethimide (Elipten—Ciba). Chemically, it is α-(*p*-aminophenyl)-α-ethyl glutarimide. It is useful in all forms of epilepsy and often improves control when used to supplement other therapy. A skin rash frequently occurs during the early stages of therapy. This usually clears up, particularly if the dosage is kept as low as is consistent with control of the seizures. Initial dosage should be low and then gradually increased to the required level. If a rash appears and it does not clear within about a week, the drug should be discontinued. The drug is available in 250 mg. tablets.



AMINO-GLUTETHIMIDE

ELIPTEN (CIBA)

A new barbiturate particularly suited for the control of febrile seizures is phenetharbital (Pyrictal—Burroughs Wellcome). Chemically, it is 1-phenyl-5,5-diethyl barbituric acid. From its structure, it will be seen that it differs from barbital only in having an N_1 phenyl



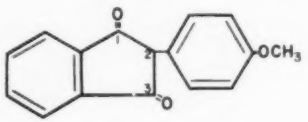
PHENETHARBITAL

PYRICTAL (B.W.)

substituent. It is said to control febrile seizures as well as phenobarbital but to be less toxic and to cause less sedation.

Anticoagulants

A new indandione derivative which depresses prothrombin formation in the liver is the compound, anisindione (Miradon—Schering). This is 2-*p*-anisyl indandione-1,3. It differs from certain other indanione anticoagulants; e.g., phenindione, in having a methoxy group in the para position on the phenyl substituent at position 2. While not a dicoumarol derivative, its structure is quite analogous and it acts in a similar manner. The advantage claimed for anisindione is that it is more predictable in its effect and can be more readily adjusted to the need of the particular patient. It is supplied in 50 mg. tablets. The initial dose is 300 mg. the first day, 200 mg. the second, and 100 mg. the third. Maintenance dosage ranges from 25-300 mg. daily (average, 75-100 mg.) but laboratory control of prothrombin time is necessary as with all such drugs. Vitamin K_1 by injection is the antidote in overdosage (prothrombin below 20 per cent).



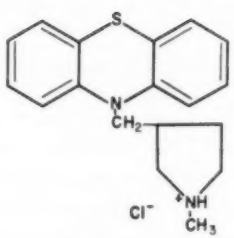
ANISINDIONE

MIRADON (SCHERING)

The drug, Athrombin-K (Purdue Frederick), released last year is the potassium salt of warfarin sodium, the latter being official in the U. S. P.

Antihistamines—Antitussive

The number of antihistamines available continues to grow with two new compounds marketed in 1960. One of these is methdilazine hydrochloride (Tacaryl—Mead Johnson). This is N-(1-methyl-3-pyrrolidylmethyl) phenothiazine. By having the terminal nitrogen in a saturated ring structure, the side-effects common to many of the phenothiazines are reduced but drowsiness is still a possibility when

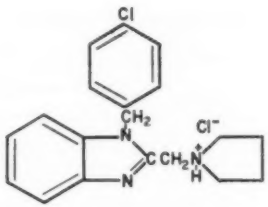


METHDILAZINE HYDROCHLORIDE

TACARYL (MEAD JOHNSON)

using it. The potentiation of sedative and hypnotic drugs is also an effect not to be overlooked. It is available in 8 mg. tablets and in a syrup (4 mg./5 ml.).

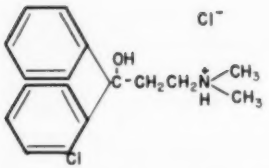
Another antihistamine recently released is clemizole hydrochloride (Allecur—Roerig). This is 1-*p*-chlorobenzyl-2-pyrrolidylmethyl benzimidazole hydrochloride. Clemizole is claimed to have a marked speed of action and to produce very little side effect. The average dose is 40-80 mg. daily in divided doses. It is supplied in 20 mg. scored tablets.



CLEMIZOLE HYDROCHLORIDE

ALLECUR (ROERIG)

The marketing of the d-isomer of chlorpheniramine maleate by Schering under the name, Polaramine, and the claims of its superiority over the racemic form have led to a similar development in the case of carbinoxamine maleate (Clistin—McNeil). This antihistamine is now also marketed in the form of its d-isomer and known as rotoxamine (Twiston—McNeil) in 2 mg. tablets and repeat-action tablets containing 4 mg.



CHLOPHEDIANOL HYDROCHLORIDE

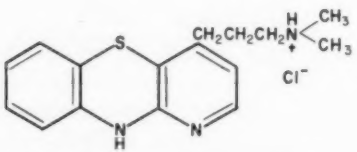
ULO (RIKER)

While not an antihistamine, a drug closely related to the well-known antihistamine, diphenhydramine, has been released as an antitussive. It is chlophedianol hydrochloride (ULO—Riker). Chemically, it is 1-phenyl-1-(1-chlorophenyl)-3-dimethylamino-propanol-1 hydrochloride. This compound developed originally by Farbenfabriken Bayer Laboratories in Germany has also been studied in this country by SchenLabs under their experimental number SL-501. Its antitussive action has been demonstrated to be comparable to that of dihydrocodeinone and to have a considerable duration of action. It also has a local anesthetic effect in the throat and has a mild antispasmodic action. It is supplied as ULO Syrup by Riker containing 25 mg./5 ml.

Psychotherapeutic Agents

In this group are considered the new tranquilizers, anorexigenics, and central stimulants including monamine oxidase inhibitors.

A tranquilizer structurally similar to but not a phenothiazine derivative is prothipendyl hydrochloride (Timovan—Ayerst). This is [4-dimethylaminopropyl-pyrido (3,2β)-1,4-benzothiazine] hydrochloride. It is useful in anxiety and tension states, particularly in the less severe conditions found in ambulatory patients. The daily dose

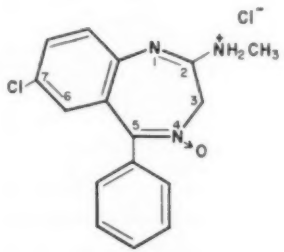


PROTHIPENDYL HYDROCHLORIDE

TIMOVAN (AYERST)

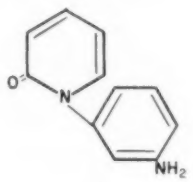
is 100-400 mg. in divided doses and it is supplied in 25 and 50 mg. tablets. As with all such drugs, it greatly potentiates central depressants such as alcohol and the barbiturates.

The drug, chlordiazepoxide (Librium—Roche), introduced early in 1960 has received considerable attention. Its chemical name is 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide hydrochloride. It is claimed to act as a tranquilizer in anxiety and tension states and, in some instances, to also have an antidepressant effect. Generally, it appears to be most useful in those conditions accompanied by tension, agitation, and anxiety—even in the more severe psychoneuroses in this category. The usual dose is 10 mg. 3-4 times daily. Side-effects are sedation and ataxia which are controlled by reducing the dose. The product is available in 5, 10, and 25 mg. capsules.



LIBRIUM (ROCHE)

The drug, amphenidone (Dornwal—Maltbie), is 1-*m*-aminophenyl-2-pyridone. It is said to be useful as a tranquilizer in anxiety

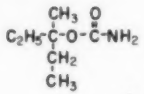


AMPHENIDONE

DORNWAL (MALTBIE)

and tension states including premenstrual tension and only rarely to produce drowsiness. It is supplied in 100 mg. tablets, the dose being 200-400 mg. 3 times daily.

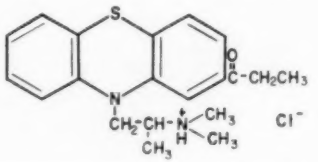
A drug closely related to meprobamate but claimed to be more potent is emylcamate (Striatran—Merck Sharp & Dohme). Chemically, it is 1-ethyl-1-methylpropyl carbamate. Emylcamate is recommended for relieving mild anxiety and tension and said not to cause drowsiness when taken in usual doses. It acts as does meprobamate by exerting an internuncial blocking action in both brain and spinal cord and again like meprobamate it has some muscle relaxing action. The usual dose is 200 mg. 3-4 times daily. It is supplied in 200 mg. tablets.



EMYLCAMATE

STRIATRAN (M.S.D.)

The phenothiazine derivative, propiomazine hydrochloride (Largon—Wyeth), is a special purpose tranquilizer for use in obstetrics and surgery to potentiate analgesics such as meperidine, to calm the patient, and to exert an anti-emetic effect. Chemically, it is 1-[10-(2-dimethylaminopropyl) phenothiazin-2-yl]-1-propanone hydrochloride. Propiomazine is administered either intramuscularly or intravenously in doses of 10-30 mg. Since it potentiates central nervous depressants, barbiturates either should not be administered with it or their dose reduced by at least one-half. Analgestics such as meperi-

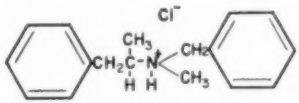


PROPIOMAZINE HYDROCHLORIDE

LARGON (WYETH)

dine and morphine should also be given in doses reduced by one-quarter to one-half in amount. Largon is supplied in 1 and 2 ml. ampuls containing 20 mg./ml.

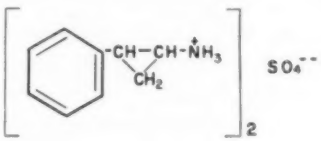
The search for more efficient anorexigenic agents continues in the hope that the ideal compound will be found. The latest modification of the amphetamine molecule to be released is benzphetamine hydrochloride (Didrex—Upjohn). This is d-N-benzyl-N-α-dimethylphenethylamine hydrochloride. Benzphetamine is reported to have less central stimulant action and less effect on the cardiovascular system than amphetamine. Its dose as an anorexigenic agent is much larger, however, being 25-50 mg. one to three times daily. In spite of its lesser effect on the cardiovascular system, it is contraindicated in severe hypertension and cardiac disease and a total daily dose of 150 mg. should not be exceeded even in normal patients. It is supplied in 50 mg. scored tablets.



BENZPHETAMINE HYDROCHLORIDE

DIDREX (UPJOHN)

The latest addition to the growing list of monamine oxidase inhibitors is tranylcypromine sulfate (Parnate—SKF). This is trans-dl-2-phenylcyclopropylamine sulfate. It was originally synthesized and tested as an anorexigenic but found to be useless for this purpose. Later, when monamine oxidase inhibitors became of considerable interest, it was tested for utility in this category and found to have



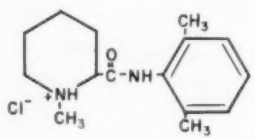
TRANYLCYPROMINE SULFATE

PARNATE (S.K.F.)

good therapeutic potential in the treatment of severe depression states. Tranylcypromine differs from other monamine oxidase inhibitors in that it is not a hydrazine derivative. This is believed to be an advantage by reason of lower toxicity. As with all drugs in this category, some time is usually required before the therapeutic effect is manifested. While some patients may show some response in 2 days, most require a week or more of treatment before improvement is noted. Even so, the response to this new MAO inhibitor is somewhat more prompt than with others. The dose is 10 mg. twice daily, morning and afternoon. If after 2-3 weeks no response appears, the dose is increased to 30 mg. daily—20 mg. in the morning and 10 mg. in the afternoon. Once response occurs, the dose should gradually be reduced to a proper maintenance level. Side-effects are occasional postural hypotension and insomnia, and the drug is contraindicated in coronary artery disease and angina. Parnate is supplied in 10 mg. tablets.

Local Anesthetics

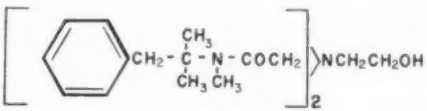
A new local anesthetic having some structural similarity to lidocaine was recently released. It is mepivacaine hydrochloride (Carbocaine—Winthrop). Chemically, this new anesthetic is d-1-N-methylpipecolic acid 2,6-dimethylanilide and, from its structure, it will be seen that, like lidocaine, it is an acetanilide derivative. Mepivacaine is an all-purpose local anesthetic and is supplied in 50 ml. multiple-dose vials containing either a 1 or 2 per cent solution for use in infiltration anesthesia or in nerve block and in a 1 per cent solution for caudal and peridural block. It is claimed to be more potent, more rapid, and more prolonged in its effect than either procaine or lidocaine and to be more stable and less toxic.



MEPIVACAINE HYDROCHLORIDE

CARBOCAINE (WINTHROP)

A special purpose local anesthetic is seen in the drug, oxethazine. This is N,N-bis (N-methyl-N-phenyl-*t*-butylacetamide) betahydroxyethylamine. As a local anesthetic on mucous membranes, it is slow in onset of action but quite prolonged in its effect and effective in very low concentrations. Under the name, Oxaine (Wyeth), it is marketed using Aluminum Hydroxide Gel as the carrier, each 5 ml. containing 10 mg. of oxethazine. The product combines the well-known antacid, protective properties of aluminum hydroxide with the prolonged local anesthetic action of oxethazine and it is used in gastritis and other gastrointestinal conditions accompanied by pain and not relieved by antacids alone. The recommended dose is 1-2 teaspoonfuls 4 times daily—15 minutes before meals and at bedtime —taken preferably undiluted. It is supplied in 12 fluidounce bottles.



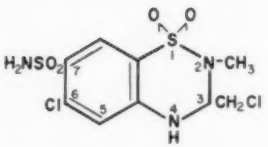
OXETHAZINE

OXAINE (WYETH)

Diuretics

The success of chlorothiazide and hydrochlorothiazide as saluretic agents and antihypertensives continues to stimulate research aimed at developing more effective drugs in this category. Several modifications of the chlorothiazide molecule have been produced, clinically tested, and marketed. Some have increased potency on a milligram for milligram basis but whether they possess any distinct therapeutic advantage such as reduced potassium loss is not clearly established.

One new sulfonamide diuretic is methylchlothiazide (Enduron—Abbott). This chemically is 2-methyl-3-chloromethyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide. It differs from hydrochlorothiazide only in a chloromethyl substituent at position 3. This difference in structure does potentiate the drug and it is claimed to have approximately 20 times the potency of hydrochlorothiazide. There is some evidence that it also causes less potassium loss but this is hard to assess since there is a marked variation in the

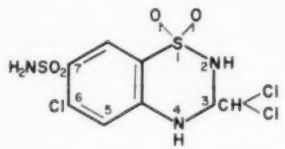


METHYLCHLOTHIAZIDE

ENDURON (ABBOTT)

degree of hypokalemia produced in patients under therapy with any of the thiadiazide diuretics. Methylchlothiazide is useful in the usual cases responding to such treatment such as the edema of congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension and that accompanying adrenal steroid therapy. It is also of value in the treatment of hypertension. The usual adult dose ranges from 2.5-10 mg. daily. To maintain an edema-free state or as an adjunct in the therapy of hypertension, a dose of 2.5-5 mg. is usually adequate. Enduron is supplied in 2.5 and 5 mg. tablets.

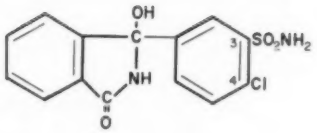
A second thiazide diuretic and one very closely related is trichloromethiazide (Naqua—Schering). This differs from the compound just discussed only in having a dichloromethyl ($-CHCl_2$) substituent at position 3 instead of a chloromethyl ($-CH_2Cl$). It appears to be of about the same potency or possibly slightly greater and it is supplied in 2 and 4 mg. tablets.



TRICHLOROMETHIAZIDE

NAQUA (SCHERING)

The third sulfonamide diuretic released last year is not a benzothiadiazine derivative. It is chlorthalidone (Hygroton—Geigy). Chemically, this is 3-hydroxy-3-(4-chloro-3-sulfamylphenyl) phthalimidine. This new drug possesses the saluretic action of the benzo-



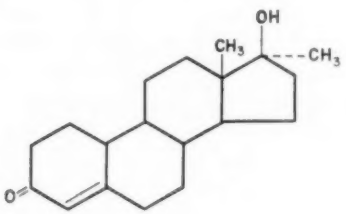
CHLORTHALIDONE

HYGROTON (GEIGY)

thiadiazines but differs in that its action is more prolonged. It is claimed to act when other similar drugs fail and to cause little or no potassium depletion. Its long duration of action makes possible maintenance of the patient on 3 doses a week. Initial therapy requires from 50-100 mg. daily, sometimes up to 200 mg. Maintenance therapy is adjusted to the patient's need and requires only 3 doses weekly provided that not more than 200 mg. is given any one day. Hygroton is supplied in scored 100 mg. tablets.

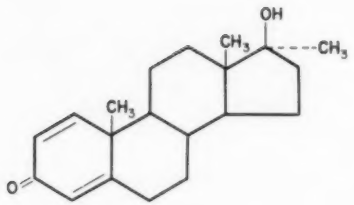
Steroids

Interest in potent progestins continues not only because of their use in maintaining pregnancy and in certain menstrual irregularities but also because of the final approval of the Searle product, Enovid, as an oral contraceptive acting by suppressing ovulation. A potent progestin under experimental trial and belonging to the 19-nor (no CH_3 at 19) group is the Syntex product, Methalutin. Some reports in the literature have suggested the possible implication of these 19-nor progestins in the masculinization of the fetus when used to maintain pregnancy.



17α-METHYL-19NOR-TESTOSTERONE

METHALUTIN (SYNTEX)

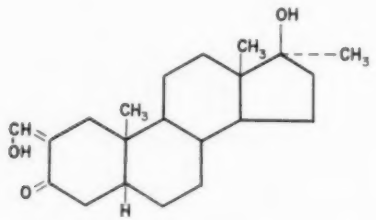


METHANDROSTENOLONE

DIANABOL (CIBA)

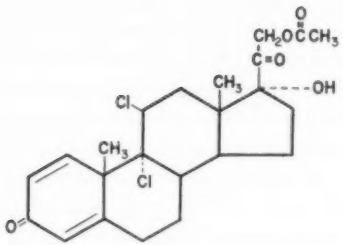
Two new anabolic steroids were marketed in 1960. One of these is methandrostenolone (Dianabol—Ciba). This is 17α-methyl-17β-hydroxyandrosta-1,4-diene-3-one. It differs from methyltestosterone only in having Δ_1 unsaturation. It is used to promote positive nitrogen balance in debilitated states such as following surgery, trauma, burns, etc. and in geriatrics. It is contraindicated in prostatic carcinoma and when there is liver impairment. As might be expected, continued use may cause a mild androgenic effect. The dose is 5-10 mg. daily (twice this may be given briefly in initiating therapy). It is supplied in 5 mg. tablets.

A second anabolic steroid is oxymetholone (Adroyd—Parke Davis). This is 17β-hydroxy-2-hydroxymethylene-17α-methyl-androstan-3-one. It differs from methyl testosterone in lacking a double bond at C #4 and having a hydroxymethylene substituent at position 2. It is supplied as 10 mg. scored tablets.



OXYMETHOLONE

ADROYD (P.D.)



DICHLORISONE ACETATE

DILODERM (SCHERING)

In the field of anti-inflammatory steroids (glucocorticosteroids), there were few new developments. One interesting new compound was released for topical use; namely, dichlorisone acetate (Diloderm—Schering). The chemical name for this is 9α,11β-dichloro-$\Delta^{1,4}$-pregnadiene-17α,21-diol-3,20-dione-21-acetate. The most interesting points about this are the chlorine substituent at position 11 where one normally expects a hydroxyl and the claim that it is both remarkably effective topically but not absorbed through the skin. It is available as a foam aerosol, a spray alcohol, and a cream—both plain and with neomycin (Neo-Diloderm).

Biologicals

Among the more important new biologicals marketed in 1960 was a new highly purified poliomyelitis vaccine (Purivax—Merck Sharp & Dohme). This is the Salk-type of vaccine but it differs from that previously available (1) in being much more highly purified, (2) may be given in fewer and smaller doses, (3) achieves immunity in a shorter time, and (4) does not vary in potency from lot to lot. The usual Salk-type of poliomyelitis vaccine is sometimes, if not always, contaminated with monkey antigen which is eliminated in this new product. It is also of such increased potency that only a 0.5 ml. dose rather than a 1 ml. dose is required and only 2 injections given 1 month apart are needed rather than 3 or 4 given over a period of 8 months. It is recommended, however, that a booster dose of 0.5 ml. be given 7 months later for maximum effect. After 2 such injections, immunity is achieved in 90 per cent of those receiving it. The purification process used in producing Purivax involves precipitation of

the virus with nucleic acid at a low pH followed by enzymatic digestion using desoxyribonuclease and ribonuclease and some subsequent steps resulting in the preparation of essentially pure virus. It is from this purified virus that the vaccine is then made using, of course, all three types. A number of other refinements in the process are also involved in making this improved vaccine.

Another new biological is glucagon introduced by Eli Lilly & Co. This is a polypeptid hormone present in the pancreas which raises the blood sugar level in hypoglycemic states by increasing phosphorylase activity, the latter being concerned in the conversion of liver glycogen to glucose. Glucagon is useful in treating insulin shock in diabetic patients and also in terminating insulin shock when induced in phychiatric therapy. Glucagon offers many advantages over the use of glucose in treating hypoglycemic shock. Recovery is gradual and smooth and only a small dose is required; namely, 0.5-1 mg. parenterally, in most cases.

Glucagon hydrochloride (Lilly) is supplied as a dry powder in ampuls containing either 1 mg. or 10 mg. together with an appropriate diluting solution in a separate ampul.

A number of other interesting developments in the field of biologicals might be mentioned. ACTH has been synthesized, the product containing 23 amino acids in its polypeptid molecule and a molecular weight of 3200. It is said to have all of the biological activity of the natural hormone. Another promising product is a measles vaccine prepared in one instance using live virus and, in another, an inactivated virus. In the case of the live virus vaccine, it has been used not only by injection but also as a spray in the nose. Which type of product, live or inactivated, will eventually be selected as the better is not yet established.

Enzymes

Enzymes continue to command considerable interest in their possible clinical applications. One such preparation not new in 1960 but receiving more attention is pancreatic dornase (Dornovac—Merck Sharp & Dohme). This is a preparation of deoxyribonuclease extracted from beef pancreas. It has the property of acting upon deoxyribonucleoprotein such as found in purulent material causing its depolymerization and changing it to a more fluid, less tenacious liquid. It is administered by aerosolization in solution into the respiratory

tree for the treatment of purulent tracheobronchitis, bronchiectasis, abscesses, and similar conditions where it thins the sputum and allows antibiotics administered with it to reach the area of infection. Dornovac is supplied as a lyophilized powder with 2 cc. of a suitable sterile diluent.

The release of fibrinolysin in 1959 by Ortho as Actase was followed shortly thereafter by a similar but not identical product, Thrombolysin (Merck Sharp & Dohme). Both are prepared by the action of streptokinase on profibrinolysin isolated from human plasma and are of great value in the resolution of clots, the reopening of venous channels, and the more rapid control of pain and swelling in thrombophlebitis. It is also of value in pulmonary embolism and in certain types of arterial thrombosis.

A very potent cellulose digesting enzyme isolated from *Aspergillus niger* is now available as Cellase-1000 (Wallerstein). It depolymerizes cellulose polysaccharides attacking the chains at the 1,4 β linkage of the glucopyranose units. Cellase 1000 would seem to offer promise as a digestive enzyme and to be particularly useful in promoting the digestion of certain vegetable products known to cause digestive difficulties in many persons.

Diagnostic Aids

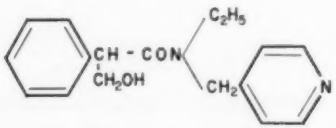
Two new radiopharmaceuticals made available by Abbott Laboratories provide more efficient and improved diagnostic aids. One is Racobalamin-57 and the other is Radio-Hippuran.

Racobalamin is cyanocobalamin (B_{12}) with a cobalt-57 label. It is recommended in place of cobalt-60 or cobalt-58 labeled cyanocobalamin in performing the Schilling test which is a method for diagnosing pernicious anemia. In the Schilling test, the patient swallows a small measured amount of the labeled cyanocobalamin. Two hours later, a flushing dose of B_{12} is injected and the patient instructed to collect a 24 hour sample of his urine. The amount of radioactive material in the urine is a measure of the efficiency with which the orally ingested B_{12} was absorbed. When using Racobalamin-57, this is measured in a scintillation detector. Labeling the B_{12} with cobalt-57 rather than cobalt-58 or cobalt-60 results in much less total absorbed radiation dose to the liver since cobalt-57 has only one low energy gamma ray, no beta particle, and a shorter half-life.

Radio-Hippuran is used in diagnosing unilateral kidney disease as a cause of hypertension. It is supplied as a sterile, pyrogen-free solution of radio-iodohippurate sodium (I^{131}). When injected intravenously, it is rapidly cleared by the kidneys. The difference in functioning of an impaired kidney as compared with a normal one is measured using two matched scintillation probes which are placed at right angles to the back, centered over the kidneys. Each probe is attached to a ratemeter and a rectilinear recorder is employed to prepare a graph of each kidney's performance. Radio-Hippuran is cleared by the kidneys faster than other labeled compounds; thus, differences between the kidneys are magnified and testing time reduced.

Miscellaneous Drugs

In this section are included a number of new drugs worthy of mention. A new rapidly acting mydriatic and cycloplegic with a short duration of action is bis-tropamide (Mydriacyl—Alcon). This is tropic acid-N-ethyl-N-(gamma picolyl) amide. It is supplied in a 0.5 per cent and 1.0 per cent solution.



BIS-TROPAMIDE

MYDRIACYL (ALCON)

A drug specifically intended for the management of the extrapyramidal reactions seen frequently as a side-effect when using phenothiazine derivatives is marketed by Knoll Pharmaceutical Co. as Akineton. It is 3-piperidine-1-phenyl-1-bicycloheptenyl-propanol-1. It is used in a carefully regulated dosage and supplied as 2 mg. tablets and ampuls containing in 1 ml. 5 mg. of the lactate.

Quinidine polygalacturonate is marketed as Cardioquin by Purdue Frederick and claimed to be better tolerated when given orally for arrhythmias than the sulfate. Each tablet contains 275 mg. equivalent to 200 mg. of the sulfate.

Arginine glutamate (Modumate—Abbott) is now available for the treatment of ammonia intoxication as seen in hepatic coma. It is administered intravenously and is supplied in a 100 ml. container for subsequent dilution with dextrose solution prior to slow intravenous infusion.

The use of nicotinic acid in hypercholesterolemia is well-known. Its aluminum salt (Nicalex—Walker Laboratories) is claimed to cause less flushing and gastrointestinal distress. Nicalex is supplied in tablets containing 625 mg. equivalent to 500 mg. of nicotinic acid.

Sorboquel is a new product for the control of diarrheas and is marketed by White Laboratories. It consists of a cross-linked acrylic acid copolymer and an anticholinergic drug, Thihexinol. The acrylic acid copolymer called Polycarbophil is not absorbed and exerts a water-binding action only in the intestine, thus reducing fluidity of the stools. Each tablet contains 0.5 Gm. of the polymer and 15 mg. of the anticholinergic drug named.

Monalium hydrate (Riopan—Ayerst) is a new antacid containing a special hydrated magnesium aluminate which provides prolonged acid-consuming power without producing an alkaline pH. It is available as both 400 mg. tablets which are swallowed not chewed and as a suspension containing 400 mg./5 ml.

Finally, in acute kidney failure and certain poisonings; e.g., barbiturate intoxication, a new technique has been developed known as peritoneal dialysis. In this technique, the living peritoneal membrane serves as the dialyzing membrane rather than using the so-called artificial kidney. Two liters of a special solution (Inpersol—Abbott; Dianeal—Baxter) are introduced into the peritoneal cavity by catheter. It is allowed to remain there for an hour during which time waste products or toxic substances normally excreted by the kidneys pass into the solution. It is then drained off carrying the waste material with it. The process is then repeated over and over.

THE UNCHERISHED REWARD *

By Edmund R. Beckwith, Jr.**

THERE have been many occasions in recent months when those of us engaged in the art and commerce of pharmaceutical science and marketing have been caricatured as money-changers in the temple of the humanitarians. Like most caricatures, the picture has been drawn for effect rather than for accuracy. Unfortunately, even we who are the subject of the fantasy sometimes react to the sharp lines and deep shadings as though they were real. We cloak ourselves in despondency or become bewildered or lash out in wounded anger. This is too bad, for never has our industry been such an exciting place to be and seldom has there been more reason for optimism about the future.

Slowly, we are coming to the recognition that we must distinguish actions which would jeopardize our principles from other actions that would modify the mere habits or methods of accomplishing an end. Little by little, we are coming to the recognition that we may be easily distracted from the fundamental forces which are carrying us in one direction while we too eagerly pay heed to the peripheral and transient episodes of day by day politics or commerce which seem to draw us in other directions. The problem is to recognize the mainstream.

In the broad consideration of health care, the most fundamental force is toward more complete, more effective, and more expensive management of the sick. Argue as we may about any one aspect—how to reallocate nursing time—how to build more efficient hospitals—how to employ electronic devices to reduce human factors—how to prevent illness rather than treat it—the basic factors are an improvement in the quality of care, an increase in its complexity, and an upward climb in costs. In the more limited area of medical care occupied by the manufacture, prescribing, and dispensing of pharmaceuticals, there is a comparable truth: every major influence supports a theory of *more* expensive, not *less* expensive drugs.

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* Presented at Third Annual Pharmacy Congress, College of Pharmacy, St. John's University, Jamaica, New York, March 17, 1961.

** President, Syntex Laboratories, New York, N. Y.

We are moving stage by stage toward more powerful and more sophisticated drugs. It is precisely this evolution toward more complex chemistry and more involved biologic study which, while it may mean statistically fewer new drugs, is the major hope for important advances and the greatest factor in higher future costs. Whether the Food and Drug Administration continues to ask for more and more data is not really the point—certainly we at Syntex have been asked for nothing unreasonable or extraneous—it is simply going to take longer periods of time, more highly trained personnel, more delicate equipment, and a great deal more money before anyone will be able to decide what a new compound does and whether it should go to the market place.

It is even likely that an increasing portion of pharmaceutical research will become less product oriented. One eminent scientific advisor to our organization commented recently, looking back over two or three decades, upon the overbalance of withdrawals from our bank of fundamental knowledge against the rate of our deposits. How apt this is, for, unless we wish to settle merely for drugs of the same general characteristics as those now on hand, research must move more deeply into the expensive and elusive shadows of the biological sciences. It is for this reason that many hundreds of thousands of dollars will be spent in the new Syntex Institute for Molecular Biology in the next few years. It is for this reason that pharmaceutical research may move more and more into genuinely fundamental areas. It may be that new balances of knowledge are needed before new advances can be obtained. Ergo: research expenses will go up, not down.

It is so easy to forget how far ahead, in many therapeutic areas, our base lines have moved in recent times. In half a dozen years, a handful of drugs for mental conditions have become the standards of measurement. A decade ago, they did not exist. Now, any hopeful new compound requires literally thousands of patient histories, monumental toxicity comparisons, and tedious metabolic analysis simply to s[illegible]ether it is only just as good, much less better, than the existing and ingrained standards.

Consider the same problem in anticoagulant therapy, in drugs for ambulatory cardiac patients, in antibiotics, in enzymology. Even in some areas of cancer chemotherapy, we already have well-established standards which demolish hundreds of hopeful new compounds,

and this—one must observe—is still an infant area of therapy. The point is, of course, that only the completely unsophisticated can escape the fact that, while the drugs prescribed by the physician and dispensed by the pharmacist today are miraculous, they are the drugs of the *past* not of the *future*. While pharmaceuticals are not the whole promise for better health, nor even the dominant part of the promise, the output of future new drugs will be an integral part of tomorrow's progress. Only the heedless could believe that tomorrow's new gains will come with less effort and less cost and less good fortune than our successes of the past. When measured against the powerful influence of this basic truth, some of the conflicts which we think of as problems of the day recede into proper perspective.

It is difficult to see the generic-name issue continuing to be worth much discussion, for the demands of necessary manufacturing facilities, more intricate and complicated quality control, the effect of the New Drug Application procedure, and the costs of minimum distribution will tend to reduce the significant areas in which the generic-name manufacturer can gain his economic short-cut. Long-term, the formulary system, whether hospital or welfare agency, is likely to become less meaningful. For one thing, should the FDA turn toward a consistent and continuous appraisal of hospital operations, that would have one effect. Because the formulary is essentially a device which gives greater weight to inventory control than to adequate and swift support of medical care, it would probably die one day of its own accord; but this demise will certainly be hastened by the development of drugs which become more subtle in both potency and precision of action. In the same way, it is to be seriously doubted that we can afford much further concern over what type of outlet sells aspirin, laxative, or antacid tablets. One should expect that tomorrow's new pharmaceuticals will rarely carry an over-the-counter label. While there will probably occur from time to time some outstanding proprietary marketing successes, these will not affect the mainstream of really new prescription drugs. Similarly, the emotion-fraught issues involving variations of cooperative pharmacies, whether union, fraternal, or mail-order, should tend to become less and less of consequence for the weight of public recognition will ultimately focus on the simple axiom that the more potent the drug the more intimate should be the communication among physician, pharmacist, and patient.

The deep trend toward more potent and more expensive drugs has been with us for some time. Its projection into the future simply indicates an acceleration from a beginning which came nearly twenty years ago. Hence, we come to consideration of possibilities for the future. If it will, the profession of pharmacy can move to a new level of public dignity. The objective: a thorough and up-to-date knowledge of pharmacology. The method: widespread and regular post-graduate study. The cost: a great deal of time and effort. The gain: an honest service to physicians. That we have not yet accomplished very much in this respect merely signals the opportunity ahead. One should not easily pass by the question of required post-graduate study in pharmacy for, let us recall, this is largely a post-war development in medicine. If it will, retail pharmacy can move toward new areas of service. Improvement in the swift, widespread availability of new drugs is badly needed. Specific organized efforts to collate new product data for physicians exist in relatively few places, and, for patients, one almost never sees clean, well-run displays of service literature, unless tied in with specific counter display merchandise.

If it will build upon its professional strength, pharmacy can continue to provide the thousands and thousands of dispensing establishments needed to serve 180,000,000 people almost around the clock. Sickness follows no time-table. Emergency knows no time-out. Whether 40 thousand, 50 thousand, or 70 thousand retail pharmacies are needed, no one knows. But let the clock strike and, close at hand, appropriately staffed, and completely stocked, the neighborhood pharmacy is as vital as any community service. Clearly, the fundamental tides favor a bright future for pharmacy. There is reason for optimism. But we need realism, too, and, in the field of economics, that means a willingness to break away from some of the shibboleths of the past.

One of the encouraging developments of recent years is the number of responsible and thoughtful leaders in pharmacy who are entertaining new ideas. True, no one yet seems to have come up with a panacea, but there is a spirit of adventure which at least entertains the novel, a spirit which inspects the new before casting it aside, and, most importantly, a spirit which accepts the interrelationships of all parts of our industry. This willingness to look ahead must apply to manufacturers and to wholesalers as well as to retailers. This

is the background philosophy which led to the development of the unusual characteristics in the Syntex distribution plan. Shortly, the Syntex program of Gradient Discounts will become operative. From wholesale list price per unit, depending upon the price range of the unit, the wholesaler will receive discounts of 17.5% on the most expensive items, 20% on units of intermediate price, and 22.5% on pharmaceuticals in the least expensive category. Clearly, we have carefully considered the inherent costs of distribution, the inescapable charges of time, investment, and professional care, and are reflecting the fact that, on one hand, there are distinctions between different preparations in the economics of distribution and, on the other, that even an inexpensive unit must be able to move from manufacturer to patient without loss to the intermediaries in its course.

At retail, we are not going to suggest prices for prescription preparations. Again, there are dramatic differences in the operations of pharmacists from one section of the country to another and from one part of a city to another. The final cost to the patient should reflect the pharmacist's own professional analysis of his individual professional services. Obviously, it is our belief that the pharmacist would do well to appraise the possibilities of a system similar to the Gradient Discount concept for, as manufacturers, we are preparing to assume a comparable posture in our own pricing practices.

Has Syntex produced a miraculous cure for the economic irritations of chronic medication? Have we devised a fool-proof method for insuring distribution of low-cost items? That is to be seriously doubted and, in fact, is probably not important. What is important is that all of us are able to attempt innovations. We are able to watch and to appraise and to test other new ideas if need be. We must search for new methods in the recognition that the comfortable framework of the past may not serve the purpose of the future. But most of all, we must be continuously aware of the fundamental forces which will shape our affairs in the future. If we dissipate our strength in trying to salvage peripheral causes, the mainstream will sweep past us. But, if we are adventurous in trying to adapt ourselves, we can view the future with more optimism than ever before.

BOOK REVIEW

Chopra's Indigenous Drugs of India, 2nd Ed. By R. N. Chopra, I. C. Chopra, K. L. Handa, and L. D. Kapur. 816 pp. U. N. Dhur and Sons, Calcutta, 1958.

Reference works on Indian medicinal plants and drugs have until recently been all too few. This new edition of Chopra (revised from the first edition of 1933) is generally a work of high quality. Over 7,300 common vernacular and popular names are indexed, while some 2,700 scientific names are indexed. The chemical treatment appears quite thorough, with abundant references to the Indian, European, and American literature. An addendum of eleven pages brings the literature cited up to 1957.

The work is divided into four parts, each having numerous sections: Medical and economic aspects of Indian indigenous drugs (48 pp.); Potential drug resources of India: Pharmacopoeial and allied drugs (210 pp.); Drugs used in the indigenous medicine (some 2,000 drugs with alleged properties are cited, 220 pp.); Indian Materia Medica (131 pp.); and Common bazar medicines of India (covering 31 pp.). Sections of the Indian Materia Medica include: vegetable products, inorganic products, animal products, poisonous plants, dermatitis producing plants (some 74 spp.); reported abortifacient and emmenagogue plants (50 spp.); insecticidal and insect-repellant plants (73 spp.); reputed piscicidal plants (87 spp.); plants containing poisonous principles (hydrocyanic and cyanogenetic glucosides, arsenic, oxalic acid, and such barium containing sp. as *Juglans regia, Nicotiana tabacum, Prunus avium, Ulmus campestris*); those having antiseptic properties (240 spp.); alleged anti-tubercular properties (103 spp.); considered useful in cholera and prolonged fevers (enteric group) (36 spp.); anti-dysenteric properties (188 spp.); plant remedies used in snake-bite (over 300 spp., but none found to be efficacious in controlled animal experiments of Caius and Mhaskar,

1931); used in scorpion-sting (some 400 spp., none of which have been found effective experimentally); essential oil bearing plants; medicinal lichens; medicinal ferns; and edible and poisonous mushrooms. The authors discuss the preparation of an *Indian Pharmacopoeia* based on the Indian Pharmacopoeial list of 1946, which contains more than three hundred vegetable drugs of Indian origin. The first edition of this was issued in 1955.

The problem of adulteration is considered in some detail. Reference is made to a survey by Harada (1951) of about twenty commonly used drugs collected in the market all over India, where practically all of them were highly adulterated. Drug legislation has improved the quality of medicinal preparations of Western medicine on the market in India, but the drugs used in the Indigenous Systems are not as yet so controlled. The authors state that adulteration has destroyed faith in drugs of Indian origin formerly of high reputation in European practice; e.g., *Cannabis indica*, because it is not of the same standard of quality as in former years and *Holarrhena antidysenterica* (through the substitution of worthless barks) has lost its position as a specific in dysentery.

Production *capacity* of certain pharmaceuticals is provided; e.g., Quinine, one million lbs. per year; Caffeine, 20,000 lbs. per year; Strychnine, 15,000 lbs. per year. It is noted that about 75 per cent of the *British Pharmacopoeia* alkaloids can be produced from plants grown in India. Vitamin A (Shark liver oil) *capacity* is listed at 5,500,000 I. U. *Actual production* figures for certain synthetics are: sulphathiazole, 4 million lbs.; sulphapyridine, more than 50 thousand lbs.; and sulphadiazine, 2 million lbs. The authors state that for many of these items production is sufficient for domestic needs, and there is also surplus for export. There are, however, deficiencies in antimalarial and sulpha drugs, and antibiotics.

Comments on the native use of crude drugs are of interest. The utility of the Western Medicine to the great masses of people in India has been limited by reason of its costliness. The average villager demands medical advice costing a few annas and the treatment costing even less. A bottle of medicine containing such purified drug preparations, and which may last only a few days, costs twelve annas to two rupees which is far beyond the means of the average Indian. Some examples cited include: the total alkaloids of the Cinchona bark are just as effective as the purified quinine itself; total alkaloids

of Ipecacuanha have also been shown to be nearly as effective against amoebiasis, as pure emetine; the total alkaloids and the galenical preparations made from the bark of *Holarrhena antidysenterica* are better than the purified conessine, while the tincture made from *Ephedra vulgaris* is just as effective in the treatment of asthma, cardiac failure, etc., as the expensive alkaloid ephedrine.

The authors provide the value of imports (firstly from the United Kingdom, secondly from the United States) for 1949-50, 78.6 million rupees; for 1950-51, 99.4 million rupees; and, for 1951-52, 151.5 million rupees. Exports of specific drugs are given, but only through 1929 with important items being about 1.4 million lbs. of Cinchona bark; 43,212 cwt. of Nux vomica, and 46,905 cwt. of Senna—for a total value of about 4.2 million rupees.

Because of the great diversity of climates and soils in India (a greater diversity than any other continental area), efforts to grow medicinal plants have been made. Important ones such as Digitalis, Ipecacuanha, Cinchona, Jalap, etc. are already being grown. Of the non-food crops, the drugs and narcotics occupy about 2.6 million acres; i.e., 0.8 per cent of the total land area under cultivation. The government Cinchona plantations occupy some 6,000 acres. The supply of Glycyrrhiza, Ephedra, Artemisia, and Asafoetida, which were mainly the products of frontier areas of West Pakistan and Baluchistan, have been cut off. The Indian Council of Agricultural Research, through its Medicinal Plants Committee, is sponsoring the cultivation not only of indigenous plants, but of exotic genera from many countries such as *Datura, Duboisia* (hyoscyamine), *Urgine; Coriandrum, Foeniculum,* and *Heliopsis* (Pyrethrum). The need for cultivation has followed the indiscriminate exploitation during recent years of such plants as Rauwolfia, Belladonna, etc.—as well as certain condiments and spices.

In reviewing future trends in drug research, the authors note that the discovery of an effective remedy is still largely empirical and depends upon accumulated experience of centuries of trial and error, the chance observation of a trained worker, or the lucky emergence of an active compound from a large series of analogs. Modern science has greatly aided in providing techniques for separating the useful drugs from the useless. Further, it would be foolish to ignore vegetable Materia Medica because the principle of investigation involved still savors of empiricism.

Some of the monographic sections provide an excellent coverage, but it cannot always be ascertained how recent is the information. In many sections, most of the material from the first edition appears to have been retained, with new material added in some cases and in others not (e.g., in the Chaulmoogra section no literature beyond 1932 is cited). The bibliographies to the respective sections often have more recent references cited, but it is not always clear from the text just how many have been utilized, if any, in the purported rewriting. Nevertheless, the work is a most valuable reference work for the subject covered by the title.

LAWRENCE J. KING

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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